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EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1657	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/621,894	WATZEK ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 17-26 as amended (2/16/2010) are pending and under examination in the instant office action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17-21 as amended remain rejected under 35 U.S.C. 102(b) as being anticipated by US 5,165,938 (Kinghton).

Claims are directed to a drug composition for topical application as intended for wound healing wherein the composition comprises i) microparticles from activated thrombocytes and ii) extracellular matrix. The microparticles are prepared by activating thrombocytes with an activating agent selected from collagen, thrombin, calcium ionophore A23187 or C5b-9 in a liquid medium and by separating the microparticles from the liquid medium by centrifugation, filtration or chromatography. Some claimed are further drawn to the virus inactivation and/or depletion in the drug product-obtained-by-process. Some claims are further drawn to the presence of matrix materials, collagen, fibrinogen, thrombin and/or organic polymers and inorganic compounds in the drug composition. Some claims are further drawn to incorporation of biocompatible materials into the drug composition or to a metal surface treated with the drug composition.

US 5,165,938 (Kinghton) discloses a drug composition produced from blood and intended for topical application and wound healing (entire document including abstract) wherein the composition comprises "microparticles" (platelet derived growth and angiogenesis factors) that are released from platelets (same as claimed thrombocytes) after activation of the platelets with collagen and/or thrombin into liquid medium and separated by centrifugation from the platelets (col. 2, lines 20-55; col. 3, lines 25-65). The "microparticles" are mixed with microcrystalline collagens and frozen (col. 2, lines 40-50; col. 4, lines 1-40). Thus, the cited composition comprises 2 identical ingredients as required by the claimed invention including i) "microparticles" and ii) extracellular matrix as required by the claimed invention. The drug composition is made under sterile condition (col. 3, line 26). Blood is collected from normal patients that are not diagnosed with viral diseases and, thus, virus depleted or virus free. The cited patent discloses that drug composition contains growth factors PDAF and PDGF or substances promoting wound healing. The cited patent clearly teaches the growth factors PDAF and PDGF containing granules are released from the activated platelets after activation with thrombin. The cited patent teaches the use of composition in conjunction with either biodegradable dressings or with some implantable devices (col. 4, lines 32-35).

Thus, the cited patent anticipates the claimed invention.

Claims 17-21 as amended remain rejected under 35 U.S.C. 102(b) as being anticipated by US 5,185,160 (Chao) in the light of evidence by Exner et al. (Blood Coagulation and Fibrinolysis. 2003, 14:773-779).

Claims as above.

US 5,185,160 (Chao) discloses (entire document) a pharmaceutical composition suitable to treat wounds (col. 3, line 34) and comprising viral-inactivated blood platelet membrane microparticle fractions (abstract). The microparticle fractions are made by activation of platelets by repeated freezing thawing and the platelet membrane microparticle fractions are separated from lysate ("liquid" into which they had been released) by centrifugation (col. 4, lines 1-60). Exner et al. evidences the inherent fact that freezing-thawing activates platelets, for example: see abstract. The product of the cited US 5,185,160 is subjected to virus inactivation by heat treatment (abstract and col. 4, lines 40-45). Proteins and/or glycoproteins (GPIb, for example: col. 5, line 11) in the final preparation of US 5,185,160 as disclosed fall within the meaning of generic extracellular matrix materials and/or biocompatible materials. The cited preparation with microparticles is suitable for wound healing (col. 3, line 34).

Thus, the cited patent US 5,185,160 (Chao) teaches composition comprising same two components and, therefore, anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17-26 as amended remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,165,938 (Kinghton), US 5,185,160 (Chao), US 5,552,290 (Michelson et al) and US 5,697,980 (Otani et al.).

Claims are directed to a drug composition for topical application as intended for wound healing wherein the composition comprises i) microparticles from activated thrombocytes and ii) extracellular matrix material. The microparticles are prepared by activating thrombocytes with an activating agent selected from collagen, thrombin, calcium ionophore A23187 or C5b-9 in a liquid medium and by separating the microparticles from the liquid medium by centrifugation, filtration or chromatography. Some claimed are further drawn to the virus inactivation and/or depletion in the drug product-obtained-by-process. Some claims are further drawn to the presence of matrix materials, collagen, fibrinogen, thrombin and/or organic polymers and inorganic compounds in the drug composition. Some claims are further drawn to incorporation of biocompatible materials into the drug composition including titanium and apatite. Some claims are further drawn to a metal surface treated with the drug composition.

US 5,165,938 (Kinghton) and US 5,185,160 (Chao) are relied upon as explained above for the disclosure of drug compositions intended for wound healing and comprising i) "microparticles" derived from the activated platelets and ii) extracellular matrix carriers. The microparticles are derived from the activated platelets, separated by centrifugation and incorporated into the drug compositions disclosed by US 5,165,938 (Kinghton) and US 5,185,160 (Chao). The cited products are made under sterile conditions, thereby, being free of contaminants or viral infection. In particular, US 5,185,160 (Chao) teaches the drug composition is subjected to viral inactivation.

US 5,165,938 (Kinghton) teaches that the microparticles are made by activating platelets with an activating agent such as collagen. In addition, the cited US 5,552,290 is relied upon for the teaching that the platelet-derived microparticles are made by activation of platelets with

various activating agents including collagen, thrombin, ionophore A23187 and protein C5b-9 (col. 1, lines 43-45 and col.3, lines 4-13).

US 5,165,938 (Kinghton) teaches incorporation of "microparticles" derived from the activated platelets into wound dressing materials and into coating materials over the devices utilized in surgical procedures that would include at least some surgical metal devices and/or instruments.

But the cited patents are missing particular disclosure about the use of titanium, apatite and organic polymers as materials for carriers and/or medical devices. However, US 5,697,980 (Otani et al.) teaches artificial filling and prosthetic device(s) capable of adhering to tissues or to wounded tissues wherein the materials include titanium core coated with calcium phosphate (apatite) and organic polymers including polycaprolactone or polyactone. For example: see abstract; col. 2, line 26 and lines 37-40; col. 3, lines 33-45 and col. 4, lines 10-17).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to add various carriers, fillings, biodegradable materials and devices including titanium, apatite and organic polymers to modify the drug compositions taught by US 5,165,938 (Kinghton) and/or US 5,185,160 (Chao) as suggested by US 5,165,938 (Kinghton) with a reasonable expectation of success in wound healing because the claimed carriers and materials are known and used for making artificial filling, carriers and medical devices as adequately demonstrated by US 5,697,980 (Otani et al.). One of skill in the art would have been motivated to adjust carrier compositions of US 5,165,938 (Kinghton) and of US 5,185,160 (Chao) with regard to a mode of administration for the expected benefits in wound healing and/or in bleeding reduction as provided by microparticles derived from blood platelets.

The knowledge about the use of various platelet activating agents for making and collecting the platelet derived microparticles is available in the prior art as adequately demonstrated by US 5,552,290 (Michelson et al).

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicants' arguments filed 2/16/2010 have been fully considered but they are not persuasive.

1. With respect to the claims rejected under 35 U.S.C. 102(b) as being anticipated by US 5,165,938 (Kinghton) the applicants' main argument (response pages 5-7) that the process steps are critical for the product-obtained by-process and that in the process of the cited S 5,165,938 (Kinghton) "microparticles" are not separated from "aqueous fraction of the thrombocyte-free liquid medium".

This argument does not have any persuasive grounds. First, the cited US 5,165,938 (Kinghton) clearly teaches (col. 2, lines 20-55; col. 3, lines 25-65) that platelet rich plasma or PRP (plasma with claimed thrombocytes) is activated with thrombin (same activating agents as claimed), the activated platelets (same as claimed thrombocytes) release alpha granules with PDAF and PDGF (same as claimed "microparticles") and the activity of thrombin also initiates coagulation; the PRP is then subjected to a removal of platelets and fibrin by centrifugation, the

resulting supernatant is the claimed "thrombocyte-free liquid medium" which "aqueous fraction" contains PDAF and PDGF or alpha granules with PDAF and PDGF (same as claimed "microparticles"). Therefore, the structure implied by the steps of the cited method is the same as the structure implied by the steps of the cited method.

Further, it is uncertain as claimed, as argued and as disclosed in the as-field specification what in the cited platelets-free supernatant (that is derived from platelets activated by the same agent and that is separated from the activated platelets) might be present that would substantially distinguish the cited "microparticles" (PDAF and PDGF or alpha granules with PDAF and PDGF) from the applicants' "microparticles".

The as-field specification does not provide specific definitions about the chemical nature/structure and molecular weight of the claimed "microparticles" besides that they are some unidentified substances released from activated platelets. The cited patent clearly teaches (col. 3, lines 50-55) that the "microparticles" (PDAF- and PDGF- containing granules) are released from activated platelets by activation with the same activating agent (thrombin) as required by the claimed invention and when read in the light of specification. Moreover, the cited document also encompasses further steps of separation of "microparticles" from supernatant by teaching "isolated" protein PDGF and its sub fractions (col. 3, lines 65-68).

Thus, the applicants' arguments are not found particularly persuasive with the respect of the claimed invention because the claimed product is a product-obtained-by-process wherein the final properties of the product obtained are not materially and/or functionally different from the final product of the cited patent. The properties of therapeutically active component as disclosed are the same as required by the claimed invention because the cited patent clearly teaches the

"microparticles" (PDAF and PDGF - containing granules) released from activated platelets by activation with the same activating agent (thrombin) as required by the claimed. What is present (left) in supernatant (liquid) after activation of platelets and after release of "microparticles" by platelets besides the "microparticles" themselves? Would the other components affect the final therapeutic "microparticles"-containing product? It cannot be reasonably said that the generic buffer components as disclosed might materially and structurally affect a wound healing composition. The cited patent discloses that the activating agent (thrombin) is removed from final microparticles-containing "supernatant" during centrifugation together with platelets and fibrin as result of coagulation of fibrinogen (col. 3, lines 52-62). Thus, the final product as disclosed by the cited patent does not contain substances that would affect therapeutic properties of the final "microparticles"-containing composition. Therefore, the argument whether or not a generic "liquid" or generic "aqueous fraction" is still present in the final product cannot be reasonable said as being a critical issue that might patentably distinguish between the claimed and cited products.

2. With regard to the claim rejected under 35 U.S.C. 102(b) as being anticipated by US 5,185,160 (Chao) applicants appear to argue (response pages 7-8) that the Chao's patent refers to "microparticles" that are not the same as the "microparticles" as intended for the presently claimed invention because the cited microparticles are derived from platelet ghosts whose membranes are disrupted by repeated freeze-thaw rather than activated and because the release of microparticles from activated platelets is not random but controlled process.

These arguments are not found particularly persuasive because the product-by-process claims are not limited to the manipulations of the recited steps, only the final structure implied by the steps. MPEP 2113. The final structure or nature of the claimed "microparticles" is no more than some generic compounds derived from activated platelets as claimed and they could be any and all cell components as disclosed (specification page 5, line 1). The Choa's "microparticles" are platelet membrane microvesicles (see title) that are obtained by repeated freezing-thawing cycles. The inherent fact that platelets are activated by freezing-thawing is evidenced by Exner et al., for example: see abstract. Accordingly to the Horstman's definitions (IDS reference) microparticles are membrane vesicles or membrane fractions released by platelets during activation and they have procoagulant activity and PF3 activity (see page 113, col.1, par. 1 and par. 3). The Chao's patent teaches exactly the same preparation of platelet-derived microparticles as defined by Horstman (IDS reference) that are platelet membrane microparticle fractions (col. 2, lines 26-27), that have procoagulant activity (col. 2, line 38) and they have PF3 activity (col. 3, line 18). Thus, the microparticles of Chao have the same structure or the same "moieties" as the applicants' claimed microparticles and they have the same activity as the applicants' microparticles as argued, as defined in the as-field specification and in the light of the prior art definitions. Thus, there is no reason to believe that the final "microparticles" of US 5,185,160 (Chao) might be different from the claimed "microparticles".

Applicants also argued previously that the cited process of making microparticles disclosed by US 5,185,160 (Chao) encompasses sonication and/or homogenization. Yet, the claimed method is open to additional and/or intermediate steps by the virtue of the open language "comprising". Moreover, size, molecular weight and/or structure of the claimed

"microparticles" is unknown as claimed and when read in the light of specification and, thus, the differences, if any, cannot be established to distinguish between cited and claimed products.

With regard to the claim rejection as being anticipated by US 5,185,160 (Chao) Applicants also argued previously that the claimed invention is directed to the use of "microparticles" that are separated "from the liquid medium into which they had been released. This argument was/is not convincing because the cited patent clearly discloses that the platelet membrane microparticle fractions are separated from lysate ("liquid" into which they had been released) by washing and centrifugation (col. 4, lines 1725; also see col. 2, lines 63-68).

3. With regard to claim rejection under 35 USC § 103 applicants argue that there is no suggestion, motivation and/or reasonable expectation in success for the combination of cited references (response pages 8-9). However, final nature of "microparticles" obtained from the activated platelet is not recited for the applicants' product as claimed and as disclosed. The references cited in the office action are in the same field of endeavor such as drug compositions intended for wound healing and comprising the platelet-derived microparticles and they seek to solve the same problems as the instant application and claims such as provide for the wound healing and comprising the platelet-derived microparticles, and one of skill in the art is free to select components available in the prior art, *In re* Winslow, 151 USPQ 48 (CCPA, 1966).

The argument that the substantial difference of the claimed invention is separation of "microparticles" released by activated platelets "from the liquid medium into which they had been released" does not appear to bear persuasive ground because the claimed product is a

product-obtained-by-process wherein the final properties of the product obtained are not materially and/or functionally different from the final products of the cited prior art.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova,

May 14, 2010

/Vera Afremova/
Primary Examiner, Art Unit 1657